REMARKS

Claims 43 to 47, 50, 53 to 59, 62 to 89, 96 to 99, 102 to 115 and 118 to 158 are pending in the application. No amendments to the claims or specification are proposed at this time.

Interview Summary

Applicants' representatives (the undersigned and Janis K. Fraser) thank Examiner Yvonne L. Eyler for the courtesy of the telephonic interview held on February 21, 2007. Examiner Eyler mailed an Interview Summary regarding this interview on March 2, 2007.

During the interview, the claims of the present application and related applications (U.S. Serial Nos. 10/053,535, 10/413,817, 10/439,632, 10/367,277, 10/600,182, 10/177,930, 11/401,722, 10/371,666, 10/676,280 and 10/455,564) were discussed with regard to their compliance with the enablement requirement.

Examiner Eyler explained that the Office, following an internal meeting between Examiners of the related applications, has concluded that Mayr et al. (Am. J. Resp. and Critical Care Medicine, Vol. 171, p. 354-360, 2005 (hereinafter "Mayr")), Ryter et al. (Current Op. in Pharma. Vol. 6, p. 257-262, 2006), Dolinay et al. (in *Breath Analysis for Clinical Diagnosis and Therapeutic Monitoring,* Amann and Smith, eds., World Scientific Publishing Company (2004), p. 203-236 (hereinafter "Dolinay I")), and Choi et al. (Am J. Resp. and Critical Care Medicine, Vol. 171, p. 318-1319, 2005 (hereinafter "Choi")) raise questions regarding scope of enablement for claims directed to treating human conditions with carbon monoxide (CO). Examiner Eyler indicated that U.S. Serial Nos. 10/053,535, 10/413,817, 10/439,632, 10/371,666, and 10/455,564 (applicants believe Examiner Eyler may have intended to include U.S. Serial No. 10/676,280 as well) either have or will receive Office Actions that describe the alleged enablement issues. Examiner Eyler also indicated that those issues do not apply to claims drawn to administering CO to organ donors, which claims are pending in U.S. Serial Nos. 10/600,182, 10/177,930, and 11/401,722.

Applicants believe that the present Reply is best presented in two parts: (A) a general response to the Office's concerns set forth in the Interview Summary dated March 2, 2007; and

(B) a specific response to the rejections raised/reiterated in the present Office Action, both of which are presented below.

A. Response to the Office's Concerns Set Forth in the Interview Summary Dated March 2, 2007

Applicants have described in the present specification experiments in rodent models demonstrating that inhaled CO provides increased tolerance to lethal levels of hyperoxia (a clinically relevant model of oxidative stress) and is a potent anti-inflammatory agent (using the widely-employed model of lipopolysaccharide (LPS)-induced inflammation). Applicants understand that, after an internal meeting among Examiners of applicants' numerous applications directed to CO treatments, the Office concluded that certain post-filing date publications cast doubt on whether applicants' rodent models are predictive enough to enable methods of treating humans with CO. According to Examiner Eyler, chief among the Office's concerns is Mayr[1], which purports to demonstrate that CO inhalation produced no anti-inflammatory effects in humans, contrary to the promising results applicants observed in rodent models. While it is clear that the Office has carefully deliberated about whether applicants' claimed methods meet the enablement requirement, its focus on and concern about the Mayr study – and the great weight it apparently gave to the study during its deliberations – is nevertheless misplaced and led the Office to a conclusion that ignores the realities of drug development.

Without question, the scientific community's efforts to test the efficacy of CO in treating disorders in human subjects remains in its infancy. Relatively slow progress in this area is due, at least in part, to the ethical and legal considerations inherent in any program involving testing a drug in humans. Of course, for patentability purposes, as opposed to drug development purposes, enablement might have been best demonstrated at the time of filing by testing CO in humans rather than rodents. But this was not feasible. In a good faith effort to provide direct evidence that CO is effective *in vivo*, applicants provided results based on the rodent models now being questioned by the Office. For the purposes of proving enablement of the presently claimed

[1] For the record, applicants note that Dr. Leo E. Otterbein, a co-inventor on the present application, advised the Mayr group as they were planning and carrying out the studies described in Mayr. He is not named as a co-author on Mayr.

methods, all that is required is evidence sufficient to overcome any bias in the art that a claimed method would not work. As established by the Federal Circuit in *In re Brana* (51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed Cir. 1995)), even *in vitro* results can suffice for this purpose. In providing the rodent models, applicants have clearly met their burden here.

One would be hard-pressed, and likely unsuccessful, to find a practitioner skilled in the medical sciences who would argue that rodents are perfect models for testing new drugs and entirely predictive of a drug's effect in other animals. Nevertheless, the reality is that few *in vivo* models are as widely accepted in the art as rodent models. Applicants' choice to use rodent models to demonstrate CO efficacy was reasonable and clearly not without precedent, as such models were, and still are, routinely used to demonstrate the efficacy of drugs at a stage prior to approval for testing in humans. In typical drug development plans, drugs that show promise in rodent models are subsequently tested in a step-wise fashion in larger animals and ultimately in humans. At each step of the way, some experimentation may be required by researchers to optimize dosage regimens and the like, but this is routine experimentation and not in any way "undue."

In citing Mayr, the Office has focused on what applicants believe may be the first publication to include human test data in a study of CO efficacy. Unfortunately, Mayr failed to observe modulation of cytokine production in human test subjects treated with CO. However, there are fundamental differences between the way Mayr carried out his experiments in humans and the way applicants' carried out theirs in rodents, differences so significant that they render Mayr's results essentially irrelevant to the question of whether applicants' models are predictive of results in humans. Key among those differences is the fact Mayr administered CO to humans solely as a pretreatment prior to injecting lipopolysaccharide (LPS), while applicants continued the CO treatment long after LPS injection. This will be discussed in further detail below. Thus, while Mayr's study may arguably be a useful first step in testing CO in humans, no skilled practitioner understanding the experiments would construe Mayr as somehow contradicting applicants' findings or demonstrating that applicants' rodent models are not predictive of effects in higher animals. The Office should likewise resist construing Mayr in that way. Practitioners

would, and the Office should, understand that Mayr was simply a limited first-step attempt to see whether CO affects LPS-induced inflammation in humans under one particular set of experimental conditions.

Turning now to the specifics of Mayr, applicants submit that several differences between Mayr's study and those provided in the specification, as well as shortcomings in the Mayr's experimental methods, preclude comparing the studies in a way that might reasonably lead one to conclude that applicants' rodent models are not predictive of efficacy in humans. Specifically, Mayr failed to replicate adequately in humans the experimental conditions employed in applicants' rodent experiments and designed an experiment that may have been insufficiently sensitive to detect any but the strongest anti-inflammatory effects.

First, in the rodent experiments described in the present application, applicants pretreated rodents with CO for one hour, then administered LPS, and then continued the CO treatment for the duration of the experiment (up to 16 hours) except for brief periods when the rodents were removed from the exposure apparatus to permit blood sampling (see the specification at page 28, lines 1 to 10). In contrast, the Mayr group chose to limit CO administration in their human subjects to an hour of pretreatment prior to administering LPS, with no CO at all administered after the LPS injection (see Mayr, e.g., at Fig. 1). Thus, the Mayr studies use a protocol for administering CO that is substantially different from that used in applicants' rodent models.[2]

Second, Mayr's experiments had the power to detect only a 50%-80% (or more) decrease in cytokine levels compared to control, because of marked variability in individual cytokine response (see Mayr at page 358, col. 2). This would be a particular issue if, for example, the dose of LPS used in their experiments were so high that it swamped out much of the effects of CO (see Mayr's statement at page 358, col. 2, that "we cannot entirely exclude that our inflammatory stimulus was too strong to allow detection of weak anti-inflammatory properties of

[2] On page 357, col. 1, lines 7 to 9, Mayr appears to cite a 2000 publication by the present inventors and others (Otterbein et al., Nature Medicine 6(4):1-7 (2000) (hereinafter "Otterbein")) as disclosing a one-hour pretreatment-only protocol in rodents similar to the protocol Mayr used in humans. Since Otterbein clearly describes treatment with CO pre- plus post-LPS; precisely as used in the present application (and in fact reports the same experiments), Mayr appears to have misunderstood the Otterbein disclosure.

CO."). Thus, Mayr's experiments may very well have missed lesser but still significant changes tending to confirm CO's anti-inflammatory effects.

Some of Mayr's statements illustrate that the Mayr authors themselves recognized the limitations of their study, e.g.,

> --"One may argue that we should have used higher CO concentrations in humans. Perhaps lengthening the CO pretreatment time to account for these saturations/dissociation differences might allow for a more significant effect on LPS-induced cytokine production." (page 357, col. 2);
>
> --"We cannot entirely exclude that our inflammatory stimulus was too strong to allow detection of weak anti-inflammatory properties of CO." (page 358, col. 2); and
>
> --"Although our LPS model is a well established model, variability in individual cytokine response is marked; therefore we had the power to detect only a 50%-80% lower cytokine release in the CO period." (page 358, col. 2).

Accordingly, and despite the Mayr data, Mayr sought not to discourage further clinical trials using CO, stating (at page 358, col. 2) "[a]lthough our clinical model cannot support an anti-inflammatory role for CO in a human systemic inflammation model it should not discourage further investigation of putative anti-inflammatory roles for CO in other clinical settings."

Although Mayr is an interesting study, for at least the reasons outlined above no skilled practitioner would accept it as definitively establishing that there is no correlation between the rodent models and larger animals. In fact, other post-filing date published studies in which CO's anti-inflammatory effects were observed in higher animals support the relevance of the rodent model employed by applicants. Consider, as a first example, Mazzola et al., FASEB 19:2045-2047 (2005), the full text version of which is published on-line at World Wide Web address fasebj.org/cgi/doi/10.1096/fj.05-3782fje (a copy of the on-line version is attached hereto as Exhibit A; hereinafter "Mazzola")[3]. Using a pretreatment-only protocol similar to that described in Mayr, Mazzola pretreated pigs with CO to observe CO's anti-inflammatory effects. The authors studied the effects of CO in a pig model of endotoxic shock because "this shock model

[3] Mazzola et al., FASEB 19:2045-2047 (2005) was cited by applicants in an Information Disclosure Statement filed January 29, 2006.

bears close resemblance to the human clinical entity [Acute Respiratory Distress Syndrome, or ARDS]." (page 8, lines 32-34). Briefly, the authors (including inventors named on the present application) pretreated pigs with CO (250 ppm), infused LPS, and observed the effects of CO on LPS-induced acute lung injury, which is caused by inflammation and closely mimics that observed in human ARDS patients (see Exhibit A at page 2, lines 21 to 24). Mazzola observed, *inter alia*, that CO pretreatment suppressed upregulation of IL-1β (a pro-inflammatory cytokine), augmented LPS-induced IL-10 (an anti-inflammatory cytokine) levels in the pigs' serum, blunted deterioration of kidney and liver function and inhibited leukocyte marginalization on lung parenchyma (see the Abstract of Exhibit A).

These effects are similar to those observed in the LPS mouse model provided in applicants' specification, beginning at page 26. There, LPS was administered to mice in a model of LPS-induced inflammation. Applicants administered 250 ppm CO before and after LPS injection to observe CO's anti-inflammatory effects. As in Mazzola's pig model, applicants observed evidence of reduced inflammation, including an augmentation of IL-10. Mazzola concludes (at page 8, lines 27 and 28) that "[t]hese results extend previous work in rodents where CO exposure resulted in the generation of an anti-inflammatory phenotype." Mazzola clearly suggests that applicants' rodent models are predictive of CO's efficacy in higher animals, in this case pigs.

As a second example, consider an abstract published by Bathoorn et al., *Eur Respir J* 2006; 28: Suppl. 50, 661s (attached hereto as Exhibit B; hereinafter "Bathoorn")[4]. There, the authors administered CO to humans to observe its efficacy against chronic obstructive pulmonary disease (COPD). CO (95 ppm) was administered to three COPD patients by inhalation for 2 hours per day over a 4 day period. The authors examined, *inter alia*, the effect of CO inhalation on the number of inflammatory cells in the sputum (a measure of inflammation). Inflammation as measured by the number of inflammatory cells in the sputum was found to be decreased in this study, despite the relatively low concentration of CO utilized. Specifically, the total number of inflammatory cells was reduced (-3.9 x 10^6/ml), as were neutrophils (-9.8%), and

[4] Bathoorn is cited in an Information Disclosure Statement filed herewith.

eosinophils (-0.2%). These and other results reported in the abstract led Bathoorn to conclude that "the directions of the effects of CO inhalation on both lung function and sputum inflammation are encouraging." Bathoorn notes that "These promising results have led to a formal RCT [Randomized Controlled Trial]."

Bathoorn's results in humans are also similar to results applicants described in the present application. For example, the specification indicates that inhaled CO reduced neutrophil numbers in the lungs of two rodent models, i.e., a hyperoxia model and an LPS-induced inflammation model. In both, inflammation was measured by determining the number of neutrophils in bronchoalveolar lavage samples. The specification states (at page 23, lines 3 to 11):

> Animals exposed to hyperoxia alone demonstrated an increase in neutrophil influx into the airways as assessed by bronchoalveolar lavage analysis (Figure 3) ($P < 0.007$). In contrast, rats exposed to hyperoxia in the presence of CO exhibited significant reductions in neutrophil influx ($P < 0.006$) (Figure 3). Moreover, identical experiments were performed using a second model of oxidant-induced lung injury and inflammation. Lipopolysaccharide (3 mg/kg *i.v.*) administered to rats induces profound neutrophil influx into the airways as shown in Figure 4. However, this neutrophil influx was significantly inhibited in the lungs of rats given LPS and exposed to CO (Figure 4) ($P < 0.007$).

Thus, Bathoorn's observations of CO's effects in humans appear to correlate well with those observed by applicants in rodents. Bathoorn, like Mazzola, supports applicants' position that applicants' rodent models of inflammation are reasonably predictive of CO's efficacy in higher animals. In Bathoorn's case, the efficacy of CO was demonstrated directly in humans, providing the scientific community with a report of a successful clinical study.

Accordingly, despite's Mayr's inconclusive results, the sum of the evidence suggests that applicants' claimed methods will work as described in the specification. This is a fact the Office should weight heavily in any analysis of whether the presently claimed methods are in compliance with the enablement requirement. Indeed, the Manual of Patent Examining Procedure (MPEP) §2164.02 requires consideration and weighing of all evidence in a determination of what a skilled practitioner would accept as a correlating model, stating:

> [I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

The weight of the evidence here clearly falls in favor of the applicants. Their rodent models are recognized by skilled practitioners as correlating to human treatment, and therefore a finding by the Office that the claims are in full compliance with the enablement requirement is warranted.

Finally, applicants wish to point out that any concerns the U.S. Patent and Trademark Office may have about skilled practitioners' ability to treat human patients with CO do not appear to be shared by the U.S. Food and Drug Administration (FDA) or the U.S. National Institutes of Health (NIH). The FDA has recently reviewed an Investigational New Drug Application (IND) submitted by the licensee of the present application (INO Therapeutics, L.L.C.). The IND proposed a clinical trial to investigate CO's ability to prevent rejection in renal transplant patients. The FDA has approved initiation of applicants' licensees' clinical trial.

The NIH, for its part, describes on their website at least two studies investigating human CO therapy. Attached hereto as Exhibits C and D are print-outs from the NIH's website, "ClinicalTrials.gov," which was visited by the undersigned on May 21, 2007. Exhibit C describes a Phase I clinical trial entitled "Effects of Inhaled Carbon Monoxide on Pulmonary Inflammatory Responses Following Endotoxin Instillation," which will examine in healthy human volunteers how breathing CO affects lung inflammation, induced by LPS. Exhibit D describes a Phase II clinical trial entitled "Modification of Chronic Inflammation by Inhaled Carbon Monoxide in Patients With Stable COPD," intended to determine whether CO inhalation therapy is effective in the treatment of patients suffering from stable COPD. It stands to reason that the primary investigators of these studies would have to provide to regulatory authorities and industrial review board evidence predictive of expected safety and efficacy, to even begin

recruiting human volunteers for these studies. As discussed in further detail below, the investigators in the study described in Exhibit C propose to administer CO a protocol that falls well within the teachings of applicants' specification.

Thus, the NIH and FDA clearly understand that skilled practitioners are capable of treating patients, including humans, with CO. This is an understanding that applicants respectfully submit should be adopted by the Office as well. A finding that the claims are in full compliance with the enablement requirement is completely appropriate in this instance.

(B) Response to the rejections raised/reiterated in the present Office Action

Turning now to the rejections raised in the present Office Action, applicants address each of the Examiner's rejections below.

Withdrawn Rejections

While the Examiner did not explicitly withdraw any previous objections or rejections, applicants assume that all prior objections and rejections not reasserted in the present Office Action are withdrawn. Thus, applicants acknowledge the withdrawal of the following:

(a) The objection to claim 103 for an alleged informality;

(b) The rejection of claim 64 as allegedly anticipated by, or in the alternative, obvious in view of, PCT application WO95/35105 (Herrmann et al.); and

(c) The rejection of claims 60, 61, 90 to 95, 100, 101, 116 and 117 as allegedly obvious over Maxwell et al. (*J. Pharmacol.*, 49:270-282 (1933)) in view of Campbell (*Brit. J. Exp. Path.*, 15(5):287-294 (1934)).

Rejection Under 35 U.S.C. §112, paragraph 1

Claims 43 to 47, 50, 53 to 59, 62 to 78, 89, 96 to 99, 102 to 115 and 118 to 158 (i.e., all of the claims presently under examination) were rejected as allegedly failing to comply with the enablement requirement. Applicants traverse the rejection for the reasons discussed below.

The Office Action suggests that the inventors have, through papers published after the filing date of the present application, somehow contradicted their claims about skilled practitioners' ability to treat patients with CO. Specifically, the Office Action states (at page 4):

> The prior art discloses administration of carbon monoxide as indicated in the prior Office Actions. However, in articles published by one of the inventors of the present Application after the filing date of the present Application, the therapeutic administration of carbon monoxide is still elusive. See Dolinay et al. (2004), pg. 224 (The duration and dose of exposure is still a subject of evaluation. The toxicological consequences of low dose CO application remain incompletely understood); Choi et al. (2005) (indicating in response to a letter indicating that the levels of carbon monoxide would be expect to give rise to brain damage and increasing brain damage to patients already brain damaged that "therapeutic" carbon monoxide may be a reality soon).
>
> * * *
>
> Although the Specification provides working examples directed to animal experiments and purports to disclose therapeutic doses, the later published articles by one of the inventors refutes this disclosure. As indicated above, even at the doses used toxicity would be expected and the inventor admits or acknowledges that the duration and dose of exposure is still a subject of evaluation and the toxicological consequences of low dose CO application remain incompletely understood and that "therapeutic" carbon monoxide may be a reality soon.

As a preliminary matter, applicants are uncertain what the Office means when it states that "that the prior art discloses administration of carbon monoxide." To provide a clear record, to the extent that the statement refers to prior art relevant to the novelty and/or obviousness of the claims, applicants respectfully state that the claims are novel and nonobvious for the reasons of record.

The Office appears to have misconstrued and mischaracterized Dolinay I and Choi. The Office characterizes these publications as proving that treating human patients with CO is unpredictable and has erroneously concluded that the detailed instructions and animal models provided in the specification, in combination with the knowledge of skilled practitioners at the priority date, are insufficient to enable those skilled practitioners to carry out the claimed methods. This is neither a fair construction of the two post-filing date publications at issue nor a

reasonable basis for rejecting the claims. The publications simply document the medical community's (including the present inventors') progress in bringing CO from the laboratory to the clinic and do not support the Office's enablement rejection.

The medical community's interest in CO is intense. Studies are being performed in laboratories throughout the world. Medical researchers are publishing their studies and predictions, both positive and negative, about the prospect of using CO to treat various human disorders (see, in addition to Dolinay I, Choi, Mayr, Mazzola and Bathoorn (which are all discussed above): Dolinay et al., Am. J. Respir. Crit. Care Med. 170:613-20 (2004) (hereinafter "Dolinay II"); Ryter et al., Physiol. Rev. 86:583-650 (2006); Thom et al., Am. J. Respir. Crit. Care Med., 171:1318 (2005) (hereinafter "Thom"); and Favory et al., Am. J. Resp. Crit. Care Med. 174:320-325 (2006)[5]. As with any new drug, it's neither surprising nor unusual that various laboratories, including those run by the present inventors, are publishing conflicting statements about the efficacy and safety of CO. A prime example of this is the description of a successful human clinical trial in Bathoorn as compared with the test described in Mayr, each of which is discussed above. Authors such as Dr. Augustine Choi, a co-inventor of the presently-claimed methods, are informing the community about what is needed to take the next steps in the development process. This is all routine in the arts of drug development and medicine – a vetting process typically undertaken for any drug accessible to the scientific community. Publications that essentially document this process and acknowledge the fact that the scientific community's and the FDA's review and acceptance of CO is not yet complete are not even an indication, much less proof, that any future experimentation that may be required to perform the claimed methods in humans is "undue."

The Office cites Dolinay I to support the proposition that the medical community's on-going evaluation of CO dosages and incomplete understanding of CO's toxicity proves practitioners are unable to perform the claimed methods. Dolinay I does not support that proposition. Skilled practitioners clearly can practice the claimed methods based solely on guidance in the specification, combined with the knowledge of those of ordinary skill in the art at

[5] These publications were cited by applicants in previous Information Disclosure Statements, so they are not supplied herewith.

the priority date. Dolinay I's point was that more work needs to done before CO clears the hurdles necessary for clinical application (i.e., FDA-approved use of CO in humans). The hurdles to which Dolinay I refers include political approval, regulatory approval and social acceptance (see Dolinay I at page 224). These obstacles have little to do with whether practitioners could perform the claimed methods in accordance with the specification and are similar to those that would exist for any drug that has yet to undergo rigorous clinical trials, although the social and political hurdles are exacerbated in the case of CO by the popular perception of CO as nothing more than an infamously toxic gas. A proper analysis of whether the present claims meet the enablement standard of U.S. patent law would not take any of these non-patent law "hurdles" into account. All the information needed for meeting the legal standard for enablement is provided in the specification, taken in combination with the knowledge of skilled practitioners at the time the present application was filed. Accordingly, basing an enablement rejection on Dolinay I is not warranted.

Concerning Choi, the Office appears to believe that the above-quoted title ("'Therapeutic' carbon monoxide may be a reality soon") proves that applicants have somehow implicitly acknowledged that skilled practitioners had insufficient guidance, at the time the application was filed, to carry out the claimed methods. It does not. Applicants fail to see how this statement could conceivably be construed as anything other than an acknowledgment that CO is not yet approved by the FDA as a therapeutic modality but may be so in the near future. Routine therapeutic use of CO is not yet a reality because the required clinical trials have yet to be performed. The fact that testing CO in humans is at an early stage does not support a conclusion that the presently claimed methods are not enabled. Thus, basing an enablement rejection on Choi is not warranted.

None of the comments discussed above suggests that testing CO in humans is particularly *unpredictable* as compared to testing any other compound in humans or in laboratory animals. Rather, upon reviewing the above-referenced exemplary publications, which describe both positive and negative findings about CO, something important stands out: practitioners in the medical community recognize that CO is a clinically relevant molecule that can be administered

to humans. The question explored in some of the publications, e.g., Thom and Choi, seems to be whether CO should be administered to humans, i.e., whether the dangers of CO can be minimized and whether the benefits of administering CO outweigh risk to the patient. That would seem to be a debate that could be applied to any new drug with potential for toxicity. It has no bearing on whether the presently claimed methods are patentable, and statements made by authors on either side of the debate should not be used against the claims of the present application. The references support applicants' position that, even though clinical trials and dosage adjustments may be needed before CO is deemed by the FDA to have been satisfactorily proven safe and effective enough to be marketed for the treatment of humans, skilled practitioners are presently able to administer CO to humans; they view safety studies, clinical trials and dosage adjustments as simply routine steps in the drug development process. The experimentation that may be required is not in any way "undue."

Indeed, skilled practitioners have reached the point of performing studies in humans, providing further evidence that the claimed methods are in compliance with the enablement requirement. Consider, for example, in addition to the Mayr and Bathoorn CO studies, the proposed clinical trial is described in Exhibit C. The investigators would have to know how to administer CO to humans in a relatively safe way to initiate this study, and they presumably believe there is a reasonable likelihood the study will show that CO inhalation successfully ameliorates systemic inflammation. As mentioned above, the investigators in the study described in Exhibit C will do so using a protocol that falls well within the teachings of applicants' specification. For example, Exhibit C states:

> [S]ubjects are treated with either CO or room air (placebo) for 6 hours. (Subjects in the pilot study receive treatment for only 3 hours). The gas is delivered through a cushioned mask placed over the nose and mouth. The amount of exhaled CO is measured before, during, and after inhalation of the gas.

Such a protocol is easily derivable from applicants' specification, which states, for example:

> Administration of compounds according to the present invention is generally through the mouth or nasal passages to the throat and lungs, where the CO may

exert its effect directly or be readily absorbed into the patient's blood stream. (page 14, lines 11 to 15); and

In addition to using CO as a therapeutic agent, the measurement of CO may be a useful diagnostic tool to determine whether a patient is in oxidative stress or has a condition or a disease state where CO may be implicated. In this aspect of the present invention, a patient will have his or her exhaled breath analyzed for the presence of CO. CO content in a patient's breath is measured by a CO monitor (for example, using a Logan LR2000) which is sensitive to the detection of CO from 0 to about 1000 ppm (with a sensitivity as low as 1 ppb). In this method, the subjects exhale slowly from functional FVC into the breath analyzer with a constant flow (5-6 l/m) over a 20-30 second interval. (page 16, lines 1 to 8).

Exhibit C's dosing regimen is one contemplated and taught by applicants in their specification. It is evidence that skilled practitioners, based on the teachings of the specification and the knowledge of those of ordinary skill in the art, would have been able to practice the invention without undue experimentation, despite the facts that CO is a potentially toxic molecule and that applicants' methods had not been tested in humans as of the filing date of the present application. Clearly, it is appropriate to refer to post-filing date publications to demonstrate that the claimed invention would have been operable for its intended purpose[6]. Thus, the specification as filed fully enables one of ordinary skill to practice the presently claimed methods.

At this juncture, given that the Office Action refers to certain of the *Wands* factors, applicants believe it appropriate to review in detail the legal standard for enablement and to show how that standard applies to the pending claims. The enablement requirement of 35 U.S.C. § 112 is satisfied so long as the disclosure contains sufficient information so that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). The Office must consider several factors when deciding whether or not a disclosure

---

[6] See, e.g., *Gould v. Quigg*, 3 U.S.P.Q.2d 1302, 1305 (Fed. Cir. 1987) ("As to the technical article, it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case, the later dated publication was not offered as evidence for this purpose. Rather, it was offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative.").

satisfies the enablement requirement and whether any necessary experimentation is "undue." The factors include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. *Id.* See also MPEP § 2164.01(a). Applicants respectfully submit that a careful consideration of the factors enumerated in *Wands* would lead the Office to the inescapable conclusion that skilled practitioners would be able to practice applicants' claimed invention without undue experimentation. Applicants address each factor in turn below.

(1) The Breadth of the Claims

Applicants acknowledge that the scope of the pending claims is broad in that, e.g., many of the claims don't specify the exact amount of CO administered to the patient. The fact that the claims are broad, however, doesn't necessarily mean that they aren't in full compliance with the enablement requirement. The MPEP, citing case law, supports applicants' position on this issue, stating (at MPEP § 2164.08):

> Claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art [.]
>
> * * *
>
> One does not look to the claims but to the specification to find out how to practice the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1558, 220 USPQ 303, 316-17 (Fed. Cir. 1983); *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
>
> > [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such

> as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

As applicants' invention, in the broadest sense, is the administration of CO to patients to treat various disorders, it is appropriate that applicants' claims broadly encompass those treatment methods. The detailed teachings of applicants' specification must be considered. Those teachings, along with information in the art, provide specific information (e.g., dosage regimens and the like) that a skilled practitioner might find useful to perform the claimed methods.

(2) The Nature of the Invention

According to MPEP § 2164.05(a), "The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art." In the present case, the nature of the invention is the administration of a potentially toxic pharmaceutical gas to treat a disorder.

(3) The State of the Prior Art

The state of the prior art is what skilled practitioners knew about the claimed subject matter at the time the present application was filed. In this case, as the Examiner is no doubt aware, there existed an extensive body of literature describing the toxicity (or lack thereof) of various levels of CO. The prior art teaches, *inter alia*, that (i) CO's toxic effects are primarily linked to blood carboxyhemoglobin (COHb) saturation; (ii) CO's toxicity depends on known factors (e.g., age, health, etc.); and (iii) blood COHb saturation is highly predictable and easily measurable. To illustrate, applicants present here for the Examiner's benefit just a small sample of useful articles that make up that vast body of literature.

Experimental administration of CO to humans and animals has been practiced for more than thirty years in the context of pollution studies. Stewart, 1976, "The effect of carbon monoxide on humans," J. Occup. Med. 18:304-309 (submitted herewith as Exhibit E), for

example, is a review article that summarizes the results of more than twenty experiments wherein various amounts of CO were administered to humans (Table 4) and provides a table of responses of humans to increasing levels of COHb saturation (Table 2). Stewart found that COHb levels up to about 20% induce mild neurological responses and physiological responses no greater than headaches in healthy individuals.

Furthermore, the COHb level of an individual administered a specified amount of CO for a period of time is highly predictable, and COHb level and toxic effects can easily be monitored during administration. Stewart describes predicted equilibrium blood COHb levels based on several concentrations of inhaled CO and O_2 (see Table 1). A later publication by the same author (Stewart, 1974,"The effects of low concentrations of carbon monoxide in man," Scand. J. Respir. Dis. Suppl. 91:56-62 (submitted herewith as Exhibit F)) indicates similarly that "the amount of carbon monoxide absorbed during exposure is highly predictable," and provides a chart showing predicted and experimental values of COHb accumulation over time for six CO concentrations (see Figure 1). Wright and Shephard, 1979, "Physiological effects of carbon monoxide," Int. Rev. Physiol. 20:311-68 (submitted herewith as Exhibit G) provides additional guidance to skilled practitioners regarding methods of experimentally administering controlled amounts of CO to individuals (p. 324-325) and methods of monitoring CO and COHb levels (p. 320-324). Wright and Shephard teach that COHb can be measured directly in blood or indirectly by measuring exhaled CO (pages 321-323). Vreman et al., 1995, "Carbon monoxide and carboxyhemoglobin," Adv. Pediatr. 42:303-34 (submitted herewith as Exhibit H) provide more guidance regarding the monitoring of CO in the blood and breath, and indicate that blood lactate levels may also be useful as an indirect measure of CO toxicity. It is evident from these publications and others in the field that, through routine monitoring of a patient during CO administration, the risks of toxicity can be minimized.

Furthermore, at the time the present application was filed, CO was being administered (apparently safely) in hospitals and clinics across the country in conjunction with a common test for pulmonary function. The CO diffusing capacity (DL_{CO}) test measures the permeability of the lungs to gases. In one variant of this test, the patient inhales a single breath of a gas mixture

containing 0.3% (3000 ppm) CO, holds his or her breath for ten seconds, and then exhales (American Thoracic Society, 1987, "Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique," Am. Rev. Respir. Dis. 136:1299-1307; submitted herewith as Exhibit I). The proportion of CO exhaled is measured and used to estimate the lung diffusion capacity. The CO exposure from this test is not trivial, as a study found that the patient's carboxyhemoglobin level increased by about 0.7% with each single-breath DL_{CO} test (American Thoracic Society, 1995, "Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique-1995 update," Am. J. Respir. Crit. Care. Med. 152:2185-2198; submitted herewith as Exhibit J). Yet the risk from exposing the patient to this very high level of CO is apparently deemed acceptable, in view of the perceived benefits of obtaining the test results.

As applicants mentioned above, these publications are but a small sample of the art regarding CO. The literature was thus incontrovertibly rich with information regarding what exposure to various levels of CO exposure can produce in terms of toxicity in humans and animals; ways to counter the toxic effects of CO; and methods of determining CO levels in patients, estimating CO uptake, and administering CO to patients for testing pulmonary function. This is certainly more information than typically exists, for example, in support of newly-invented cancer treatments, which not infrequently involve inherently toxic (and even poisonous) substances, yet nonetheless are considered useful.

(4) The Relative Skill of Those in the Art

In the present case, "those in the art" would have been health care practitioners, e.g., physicians. Applicants submit that health care practitioners at the priority date had a high level of skill in administering drugs (even potentially toxic ones) to patients. To illustrate, one could point to any number of highly toxic drugs, such as cancer chemotherapeutics, that are routinely and successfully administered by physicians of ordinary skill. One could also list medical gases such as oxygen (which can cause oxidative stress and lung damage) and inhaled anesthetic gases,

which can be dangerous in overly high doses. Applicants will focus on a single, particularly pertinent example: nitric oxide (NO) gas (not to be confused with nitrous oxide N_2O).

NO gas is an FDA-approved pharmaceutical agent that bears many similarities to CO. Both are colorless and odorless gases that are products of combustion and commonplace components of air pollution and cigarette smoke. Like CO, NO binds to and inactivates hemoglobin. NO has the additional danger (not found with CO) of being a highly chemically reactive molecule. NO readily reacts with oxygen (e.g., in the air) to yield NO_2, which in turn forms extremely corrosive and dangerous nitric acid when it reacts with water (e.g., in the lung). Since CO does not exhibit anything like that level of reactivity, NO gas arguably has an even higher level of potential toxicity than does CO. Yet, despite all of the potential dangers of NO, it was approved for pharmaceutical use by the FDA in December of 1999 after six years of clinical trials (see, e.g., http://www.touchbriefings.co.uk/pdf/790/ino.pdf). Since then this has become an important, lifesaving therapeutic for so-called "blue babies," i.e., newborns in respiratory distress due to hypoxic respiratory failure.[7] These "blue babies" – owing their blue color to lack of oxygen in their blood – miraculously turn a healthy pink when they inhale NO. The very real potential toxicity of NO requires careful attention to proper clinical use, but this certainly has not proven to be a barrier to widespread, successful use of NO-based therapy in hospitals around the world. This illustrates that healthcare practitioners of ordinary skill (e.g., those participating in the clinical trials) at the present application's priority date knew how to manage appropriate medical use of potentially toxic medical gases.

(5) The Predictability or Unpredictability of the Art

According to the MPEP at section 2164.03,

> the 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

---

[7] The physicians who invented the NO treatment were given the 2003 Inventor of the Year award by the Intellectual Property Owners Association for this lifesaving contribution to the medical sciences. One of their issued patents is U.S. Patent No. 5,485,827.

Given the extensive body of literature that existed at the time the present application was filed, the detailed teachings of the specification and the level of skill of practitioners in the fields of medicine and drug development, skilled practitioners would have appreciated that a CO treatment regimen might have to be routinely adjusted depending upon certain variables, e.g., the type of patient (e.g., human, dog, rat, etc.) and the size, age, and condition of the patient. However, skilled practitioners would have had no reasonable basis for doubting that the claimed methods would work, despite a potential need for such routine adjustments. Once applicants showed that the methods worked in one species, skilled practitioners would clearly have been able to predict that a similarly successful outcome would very likely be achievable in others, even though routine experimentation, e.g., to account for differences between species and disorders, might be required. Indeed, this is substantiated by the facts that Bathoorn's clinical trial was undertaken based on results observed in preexisting CO *in vivo* studies (presumably studies performed in rodent models) and that the FDA has approved applicants' licensee's clinical trial to investigate CO's ability to prevent rejection in renal transplant patients.

(6) The Amount of Direction or Guidance Presented

The specification throughout provides detailed and useful guidelines for administering CO to patients. For example, the specification teaches how to make gaseous CO compositions for delivery to a patient (see, e.g., page 15, lines 10 to 15). It also teaches how to deliver CO to patients and what variables to consider when choosing a dosage regimen (see, e.g., page 14, lines 10 to 24). Dosage amounts are also discussed throughout the specification, e.g., at page 5, lines 11 to 17, and page 11, lines 13 to 15. Applicants have clearly presented a sufficient amount of direction and guidance for skilled practitioners who wish to carry out the claimed methods.

(7) The Presence or Absence of Working Examples

The specification provides working examples (at pages 16 to 37) demonstrating that inhaled carbon monoxide can be used to treat oxidative stress and inflammation. For example,

the present application provides data demonstrating that inhaled carbon monoxide provides increased tolerance to lethal levels of hyperoxia, which is a clinically relevant model of oxidative stress. This model provides support for applicants' claims directed to treatment of conditions involving oxidative stress, and in particular, to treatments for lung diseases. Further, the specification provides a working example demonstrating that carbon monoxide is a potent anti-inflammatory agent, both *in vitro* and *in vivo*, using the widely-employed model of LPS-induced inflammation. This model supports applicants' claims directed to treatment of various conditions involving inflammation, and in particular to treatment of systemic inflammation such as that associated with sepsis.

(8) The Quantity of Experimentation Necessary

In order to determine effective amounts of CO for human or other patients, skilled practitioners will need to perform clinical studies. However, as applicants stated above, skilled practitioners in the arts of drug development and medicine routinely perform such studies to determine effective doses when bringing a new drug from the laboratory to the clinic. This is routine and reasonable experimentation. The Office has presented no evidence suggesting that a determination of effective amounts of CO, e.g., in humans, would be any less routine.

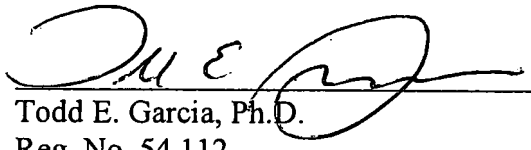
Applicants submit that a thorough examination of the specification and a rigorous application of the *Wands* factors would lead the Office to the conclusion that the present claims are in full compliance with the enablement requirement. Skilled practitioners would clearly have been able to practice the full scope of the invention recited in the claims when armed with applicants' specification and the knowledge of those of ordinary skill in the art.

CONCLUSION

Applicants request that the claim amendments be entered and that all claims be allowed. Enclosed is a check for $1020 for the Petition for Extension of Time fee for a three-month extension. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 13681-003002.

Respectfully submitted,

Date: June 1, 2007



Todd E. Garcia, Ph.D.
Reg. No. 54,112

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906